EARLY AND ACCURATE DIAGNOSIS IN JAUNDICE

M. M. Baird, B.A., B.M., B.Ch., M.R.C.P.(Lond.), F.R.C.P.[C.], E. J. Badre, B.Sc., M.D.C.M., A. Bogoch, M.D. and I. D. Maxwell, B.Sc., M.B., Ch.B.

Shaughnessy Hospital, Vancouver, B.C.

THE importance of early and accurate diagnosis in jaundice need not be emphasized. Although an accurate clinical diagnosis can be made early in the majority of cases, prolonged observation in the remainder is often necessary though undesirable. To operate on a case of hepatic jaundice is obviously inadvisable and may, indeed, be dangerous, while to allow a case of extrahepatic obstructive jaundice to persist may result in liver damage. Moreover, with an earlier diagnosis, there is a shorter stay in hospital and less cost to the patient.

When jaundice is the presenting sign, a complete history and thorough physical examination is adequate to make an early and accurate diagnosis in a large percentage of cases. This is especially true if one has a useful classification in mind and considers the possible causes. Jaundice is commonly divided into three main groups: (1) Prehepatic jaundice. (2) Hepatic jaundice. (3) Posthepatic or extrahepatic obstructive jaundice.

PREHEPATIC JAUNDICE

Although the causes of hæmolytic jaundice are numerous,[1] this condition is relatively uncommon. Characteristically, icterus is mild and there is anæmia, splenomegaly, and usually evidence of active blood regeneration. Icterus is due to the production of bilirubin at a rate greater than that at which the normal hepatic cells can metabolize or excrete it. As a result, there is hyperbilirubinæmia of the indirect type with a low value for the direct reacting bilirubin. No bile appears in the urine and, because of increased urobilinogen excretion, the urine and fæces tend to be dark. Except for those of pigment metabolism noted above, the liver function tests are normal or only slightly abnormal and there is no demonstrable pathology in the liver.[2] However, in some cases of hæmolytic jaundice, the agent which causes hæmolysis may also cause liver damage and laboratory evidence of hepatic jaundice will be present.

Non-hæmolytic prehepatic jaundice (constitutional hepatic dysfunction, physiological hyperbilirubinæmia) is due to an unexplained constitutional inability of the liver to clear the blood of bilirubin in a normal manner. According to Hanger,[3] this condition which may also be familial, occurs chiefly in a subclinical form. In overt cases, jaundice is usually noted in early youth and tends to become less striking with advancing years. Icterus is usually mild and may become deeper after exertion, fatigue or intercurrent illness. These patients are usually symptomless but may be thin, listless and subject to fatigability. There are no related abnormal physical findings and no abnormalities of the blood can be demonstrated. There is hyperbilirubinæmia of the indirect type, and the liver function tests, except for a questionably impaired bilirubin clearance, are all normal. Adequate laboratory investigation and prolonged observation are necessary to exclude other causes of jaundice. If the mild, usually scleral icterus is overlooked, the disorder goes unrecognized and symptoms may be wrongly interpreted as psychogenic in nature.

As a rule, there is usually little difficulty in distinguishing prehepatic jaundice from the hepatic or posthepatic groups.

HEPATIC AND POSTHEPATIC JAUNDICE

Assessment of clinical factors. — While of limited diagnostic importance in the individual case, it is interesting to note that in Flood's[4] series, 80% of patients with hepatic jaundice were under the age of 40, whereas 80% of patients with extrahepatic obstructive jaundice were over this age. Men are much more commonly affected with hepatitis, portal cirrhosis and extrahepatic obstructive jaundice due to carcinoma of the pancreas, whereas 71% of cases of posthepatic jaundice due to cholecystitis, choledocholithiasis and cholangitis occur in women.[3] Very important is a history of exposure to infectious hepatitis or hepatotoxic drugs, and of parenteral inoculation with human blood products in the form of vaccines, convalescent serums or transfusions of plasma or blood. The incubation period in infectious hepatitis is usually two to six weeks but may be somewhat longer in infections of low virulence. In homologous serum jaundice on the

other hand, it is from one to six months and usually two to four and one-half months.[5] The importance of noting the occupation of patients suspected of having Weil's disease and of considering exposure to amœbic infection in questionable cases of amœbic hepatitis is obvious. In an alcoholic patient, a history of hæmatemesis, or of periodic bouts of gastric disturbances such as anorexia, nausea, flatulence and occasional vomiting, should lead one to suspect portal cirrhosis. A past history of cholecystic disease and of biliary colic is obtained in the large majority of patients with extrahepatic obstructive jaundice due to choledocholithiasis. If jaundice is due to a stricture of the common bile duct, there is usually a history of a stone, or of a former operation on the biliary tract. A previous operation for malignancy suggests possible metastases to the liver and to the glands at the porta hepatis, which compress or invade the bile ducts. We have recently been confused for a time in two cases in which the jaundice was considered to be due to metastases but proved to be of the homologous serum type, following postoperative transfusions of pooled human plasma.

Weight loss. — While preceding weight loss usually occurs and may even be marked in hepatitis and in portal cirrhosis, it is very often rapid and progressive in posthepatic jaundice due to carcinoma of the pancreas.[6]

Onset. — The onset of the illness is often gradual or uneventful in portal cirrhosis and in cases of extrahepatic obstructive jaundice due to carcinomatous processes, while it is usually relatively abrupt in virus hepatitis and in posthepatic jaundice due to other than malignant causes. The importance of anorexia as a prominent, early and almost constant symptom in acute hepatitis due to any cause has been stressed by Sinclair and Farquharson.[7] Other commonly associated pre-icteric symptoms include, malaise, weakness, headache, chilly sensations, nausea and vomiting.

Pain.—Upper abdominal pain is said to occur in 56% of cases of hepatitis.[3] It is usually mild, but is occasionally severe and accompanied by right upper quadrant guarding suggestive of an "acute surgical abdomen".[5] Upper abdominal pain also occurs in a similar number of cases of posthepatic jaundice due to carcinomatous processes.[3, 7] However, biliary colic seldom occurs in posthepatic jaundice due to carcinoma of the pancreas but is very suggestive of jaundice due to choledocholithiasis. Pain in chronic pancreatitis is steady, seldom lasts less than two days and often from two to fourteen days. It starts in, or shifts to, the left upper part of the abdomen and the left side of the back and is often not relieved by one injection of morphine.[8] These features were well demonstrated in two cases of chronic pancreatitis included in this series.

Course. — Jaundice usually develops more rapidly in hepatitis than in portal cirrhosis, while it tends to develop insidiously, to deepen progressively and to be persistent in posthepatic jaundice due to carcinomatous processes. Recurring attacks of jaundice are usually due to choledocholithiasis or to chronic pancreatitis and cholangitis, with or without obstructive biliary cirrhosis. Jaundice caused by choledocholithiasis tends to be transient and of varying intensity but when due to chronic pancreatitis it is apt to persist longer and may never go completely away, lessening between attacks and deepening again with each recurrence of the acute pancreatic pain.[9] Icterus of fluctuating intensity often results from the ball-valve action of a gallstone at the lower end of the common bile duct.

Pruritus.—Pruritus is said to be present in most cases of posthepatic jaundice due to carcinoma of the pancreas, gallbladder and bile ducts,[3] but also occurs in jaundice due to other causes and is, therefore, of little diagnostic importance.

Pyrexia and pulse.—Pyrexia and pulse rate are seldom of assistance in the differential diagnosis. However, jaundice without pyrexia tends to exclude the presence of cholangitis, pylephlebitis, hepatic abscess and jaundice occurring in septicæmia, pneumonia and Weil's disease.[9] Jaundice with rigors is suggestive of suppurative pylephlebitis, hepatic abscess and cholangitis with or without suppurative cholecystitis from gallstones or from carcinoma.[9]

Tenderness.—It is generally felt that right upper quadrant tenderness occurs most frequently in hepatitis, less frequently in choledocholithiasis and seldom in portal cirrhosis or in carcinoma of the pancreas. The size of the liver is of little value in the differential diagnosis of jaundice, except that a decrease in liver size associated with delirium is indicative of progressive hepatic necrosis. In acute hepa-

titis the liver edge is usually smooth and tender. Palpation of the surface of a hard, cirrhotic liver may reveal small, cherry-sized nodules, as compared with the larger, often umbilicated lumps, occasionally palpated in a carcinomatous liver.[9] The finding of a palpable gallbladder is nearly always indicative of extrahepatic obstructive jaundice, which is usually due to carcinoma of the pancreas.

Palpable spleen.—A palpable spleen is not an uncommon finding in virus hepatitis, while in portal cirrhosis the spleen is palpably enlarged in about one-half of the cases. The spleen was palpated in two of our cases in which posthepatic jaundice was due to chronic pancreatitis and cholangitis with obstructive biliary cirrhosis. In cases of chronic posthepatic jaundice due to a stone impacted at the ampulla of Vater, the spleen is said to be palpable with considerable frequency.[10] When extrahepatic obstructive jaundice is due to carcinoma of the pancreas, the spleen is not palpable unless there is extension to involve the splenic vein.[7]

Ascites.—Ascites associated with jaundice occurs very commonly in portal cirrhosis; and may also occur in patients with severe virus hepatitis,[11] portal obstruction due to tumour, or peritoneal tumour implants. In the large majority of cases the presence of collateral subcutaneous venous circulation is good evidence of portal cirrhosis.[12] Acquired spider angiomata, nearly always indicative of hepatic jaundice, are also usually associated with portal cirrhosis.

Needless to add, other physical findings, such as abdominal, rectal, ovarian or glandular masses, will help in the determination of the cause of the icterus.

LABORATORY STUDIES

Various laboratory tests are of value in differentiating hepatic from extrahepatic obstructive jaundice. A flat film of the abdomen may reveal gallstones or pancreatic calculi possibly related to the disease process. Cholecystography is of little or no value in the presence of jaundice. Malignant lesions of the gastrointestinal tract, œsophageal varices and deformities of the duodenum due to pancreatic disease are all valuable radiological findings. Marked leukocytosis with a shift to the left in the neutrophil count is supportive evidence of a suppurative process. Leukocytosis rarely occurs in virus hepatitis. Laboratory tests in Weil's disease are useful while the identification of endamœba histolytica in the stools of suspected cases of amœbic hepatitis is strong supportive evidence. Elevated serum amylase, glycosuria, and stools containing muscle fibres and abnormal amounts of fat are highly suggestive of pancreatitis. Otherwise unexplained tarry stools in patients with jaundice should suggest the possibility of carcinoma of the pancreas invading the duodenum. The study of duodenal contents is recommended by many[2, 10, 13] as a helpful procedure in determining the cause and completeness of posthepatic jaundice and the presence of cholangitis. We successfully employed duodenal drainage to prove the presence of cholangitis in two cases of incomplete obstructive jaundice due to chronic pancreatitis.

The greater number of diagnostic difficulties are encountered in those cases of mild or moderate jaundice which tend to be prolonged. We have found certain liver function tests of definite value in distinguishing hepatic from extrahepatic obstructive jaundice.

This report deals with 30 unselected cases of jaundice admitted to Shaughnessy Hospital during the past year. The clinical diagnosis in 26 of these was confirmed either by needle biopsy, at operation or at autopsy. In the 4 remaining cases, the diagnosis of homologous serum jaundice was well established but histopathological study of the liver was not done.

Our cases consisted of:

1. Hæmolytic jaundice		1
2. Hepatic jaundice:		
Virus hepatitis—		
(a) Homologous serum jaundice	10	
(b) Infectious hepatitis	4	
Portal cirrhosis	2	
Primary carcinoma of liver (cholangioma)	1	
		17
3. Posthepatic or extrahepatic obstructive jaundice:		
Choledocholithiasis	2	
Chronic pancreatitis	2	
Carcinoma of pancreas	3	
Carcinoma of gall bladder	2	
Carcinoma of ampulla of Vater	1	
Lymphosarcoma	1	
Metastatic carcinoma	1	
		12
Total		30

The case of hæmolytic jaundice was of the acquired type, of unknown etiology and re-

covery followed removal of an enlarged spleen. The ten patients with homologous serum jaundice had received transfusions of reconstituted plasma at periods varying from 70 to 158 days prior to the onset of jaundice. Both cases of portal cirrhosis were in the terminal stages and one died a few days after admission with a superimposed hepatic necrosis. The rare case of primary carcinoma of the liver was a cholangioma associated with portal cirrhosis. The chief clinical features were mild icterus, ascites, and a palpable mass in the right upper quadrant which proved at autopsy to be a tumour mass extending from the lower edge of the right lobe of the liver. The entire liver was riddled with hæmorrhagic and bile pigmented tumour nodules and the extrahepatic bile ducts were not obstructed. The diagnosis was suspected from the microscopic study of liver tissue obtained by needle biopsy. In both cases of posthepatic jaundice due to chronic pancreatitis and cholangitis, liver tissue obtained by needle biopsy revealed evidence of obstructive biliary cirrhosis. One of the two cases of carcinoma of the gall bladder was associated with cholelithiasis. In addition to carcinoma of the pancreas, one patient had a large penetrating non-malignant pyloric ulcer. Enlarged posterior cervical and axillary glands were found in the patient with lymphosarcoma and except for those that caused obstruction of the common bile duct, the abdominal glands were not enlarged. At post mortem, only a few areas of lymphosarcoma could be demonstrated in the liver. Massive metastases from carcinoma of the stomach to the liver and lymph nodes at the porta hepatis were responsible for the last case of jaundice listed above. In all three cases in which hepatic metastases were found at autopsy, such metastases had previously been proved by needle biopsy. However, such a high proportion of positive results is not to be expected in a larger series.

In addition to thorough clinical investigation, routine laboratory procedures and x-ray studies where indicated, the following liver function tests were performed:

Test	*Method*	*Our normal values*
Total serum bilirubin	Malloy and Evelyn[14]	Up to 1 mgm./100 c.c.
Direct reacting bilirubin		Up to 0.4 mgm./100 c.c.
Urine bile	Gaelin[15]	Negative
Urine urobilinogen	Watson and Hawkinson[16]	Up to 1 Ehrlich unit per 2 hr. spec.
Stool urobilinogen	Watson and Hawkinson[16]	50 - 250 E.U./100 gm. fæces.
Total serum protein	Kingsley[17]	6.0 - 8 gm./100 c.c.
Albumin/globulin		3.4 - 6/1.5 - 3.0 gm./100 c.c. 1.3 - 4/1.
Total serum cholesterol	Bloor (modified)[18]	170 - 250 mgm./100 c.c.
Prothrombin activity and response to vitamin K.	Wintrobe[19]	80 - 100%
Serum alkaline phosphatase	King[20]	3 - 13 K.U.
Cephalin cholesterol flocculation	Hanger[21]	0 - 1 +

Tests of pigment metabolism. — Normally, hæmoglobin is broken down by the cells of the reticulo-endothelial system to bilirubin, which is of the indirect reacting type and does not appear in the urine. It enters the liver where it is modified, and accompanied by other elements of the bile it reaches the intestine by way of the biliary tract. In the intestine, bilirubin is converted to urobilinogen which is almost entirely excreted in the stool, and as urobilin (the oxidation product of urobilinogen) is largely responsible for its colour. A portion of the urobilinogen is absorbed from the bowel and carried in the portal blood stream to the liver where it is almost entirely excreted in the bile. A small amount, however, passes into the general circulation to be excreted in the urine. Serum bilirubin which has been modified by the liver is of the direct reacting type and if present in abnormal amounts, passes readily into the urine.

The qualitative study of serum bilirubin (direct, indirect) is of value in the diagnosis of prehepatic jaundice, but is of little or no value in distinguishing hepatic from posthepatic jaundice. Periodic total (quantitative) serum bilirubin estimations indicate the trend of the patient's icterus which may be of value in differential diagnosis. The total serum bilirubin level did not exceed 21 mgm. % in 16 out of 17 cases of hepatic jaundice. The patient with portal cirrhosis and superimposed hepatic necrosis and eight out of twelve cases of extrahepatic obstructive jaundice reached levels above this figure. However, as has been shown by Sherlock,[22] the intensity of jaundice is an uncertain

guide to the nature and extent of liver and biliary tract involvement and forms an unreliable basis upon which to found a differential diagnosis.

Typically, no bile appeared in the urine in the case of hæmolytic jaundice and urobilinogen was present in increased amounts in both urine and fæces. In hepatic and in extrahepatic obstructive jaundice, variable amounts of modified bilirubin are unable to reach the intestine and so enter the blood stream. As direct reacting serum bilirubin, it readily passes into the urine. In both hepatic jaundice and in persistent incomplete extrahepatic obstructive jaundice in which secondary liver damage follows, the urobilinogen which is absorbed from the bowel cannot be handled by the damaged liver cells and so passes into the general circulation to be excreted in the urine. Thus studies of pigment metabolism are of little value in distinguishing medical from surgical jaundice. In posthepatic jaundice and in the prolonged intrahepatic obstructive phase frequently encountered in hepatitis, very little or no bile reaches the intestine and as a result, there is decreased formation, absorption and excretion of urobilinogen in the urine and fæces. In four of our cases of hepatitis, this obstructive phase persisted from 1 to 2 weeks and occasionally it persists much longer. The exact mechanism of the intrahepatic obstructive phase is not known but it accounts for some of the difficulties in distinguishing between cases of hepatic and posthepatic jaundice. Daily inspection of the stools for colour is very important in following the course of patients with jaundice. A very reliable indication of complete biliary obstruction is an excretion of less than 5 E.U. of fæcal urobilinogen per 100 gm. fæces. Since complete obstructive jaundice is most commonly due to a malignant growth,[2] this test may be of value, provided that repeated examinations are performed. In the cases in which fæcal urobilinogen was estimated, the most striking results were obtained in the patient with hæmolytic jaundice and in the cases of complete extrahepatic obstructive jaundice in which it was performed. In other types of jaundice this test is of little diagnostic value.

Total serum proteins and A/G ratios.—According to Dauphinee and Campbell,[23] a characteristic disturbance of serum proteins occurs in patients with parenchymal disease of the liver. It is characterized by a rise in serum globulins, especially the euglobulin fraction which in turn is largely due to the appearance of an abnormal "13½% fraction", and a more or less corresponding fall in the serum albumen. In acute hepatitis of no more than usual severity, there is no gross abnormality of the total serum proteins but a mild decrease in the serum albumen and a definite increase in the total globulin does occur in almost all cases. In portal cirrhosis the abnormalities may be much more pronounced. No striking change in serum globulins is found in cases of extrahepatic obstructive jaundice but in carcinomatous cases, a decided fall in serum albumen is a frequent finding.

In the case of hæmolytic jaundice, the total serum proteins were 6.0 gm./100 c.c. comprised of 5.1 gm. albumen and an unexplainably low globulin level of 0.9 gm. The total serum proteins were estimated in ten cases of virus hepatitis and the albumen and globulin values in five. No abnormalities were found. The two patients with portal cirrhosis had total serum proteins of 6.3 and 5.5 gm. In both, the serum albumen was below normal and the serum globulins elevated with A/G ratios of 0.48 and 0.55. This is a characteristic finding in portal cirrhosis. The patient with primary carcinoma of the liver had normal total serum proteins with a depression of the albumen and a slight elevation of the globulin fraction with a resultant A/G ratio of 0.8. Seven patients with posthepatic jaundice had normal total serum proteins. In five of these in which the albumin-globulin values were determined, three had reversed A/G ratios. Two of these were patients with chronic pancreatitis and obstructive biliary cirrhosis in which the serum albumen was reduced and the serum globulins elevated, with ratios of 0.64 and 1. The other reversed A/G ratio occurred in the patient with lymphosarcoma and it was associated with a normal albumen and an elevated serum globulin value.

Total serum cholesterol.—This test was performed in all cases but one of virus hepatitis and one of posthepatic jaundice. According to Cantarow,[24] hypocholesterolæmia is uniformly observed in hæmolytic jaundice but in the single case studied, only one of two estimations were found to be abnormally low. There was no constant finding in the hepatic or extrahepatic obstructive groups but three significant

features were observed: (1) Values below 170 mgm. % were obtained in four cases of virus hepatitis and in one case of portal cirrhosis but not in extrahepatic obstructive jaundice; (2) Values above 300 mgm. % were found in four cases of extrahepatic obstructive jaundice and in no other condition. The cholesterol level was not related to the severity of the obstruction; (3) Normal values and levels up to 300 mgm. % occurred in the remaining cases of hepatic and posthepatic jaundice.

According to Cantarow,[25] hypercholesterolæmia is usually found in patients with uncomplicated extrahepatic obstructive jaundice and this may be of value in differential diagnosis.

Prothrombin activity and response to vitamin K.—The formation of plasma prothrombin which is essential for the coagulation of blood, occurs in the liver and depends on the absorption of vitamin K from the intestine. Hypoprothrombinæmia may occur if hepatocellular function is impaired as in hepatic jaundice, or if there is inadequate absorption of vitamin K due to the absence of bile salts in the intestine as occurs in uncomplicated posthepatic jaundice. Thus the failure to respond to parenterally administered vitamin K is considered an indication of hepatocellular damage.

The prothrombin activity was normal in six out of eleven cases of virus hepatitis. Twenty-four hours after intramuscular injection of 5 mgm. of vitamin K the prothrombin activity was below normal in three of the remaining five cases in which it was tried, indicating a poor response to vitamin K. In both cases of portal cirrhosis, the values were abnormal and a poor response to vitamin K followed. Contrary to what one would expect, the prothrombin activity was 100% in the patient with massive primary carcinoma of the liver. This test was normal in 5 of 11 cases of posthepatic jaundice and response to vitamin K was attempted in 5 of the remaining 6. Of the three in which there was a poor response, one patient had chronic pancreatitis with associated biliary cirrhosis and the other two had malignant obstruction with extensive metastases in the liver.

Serum alkaline phosphatase.—Alkaline phosphatase is an enzyme present in many body tissues and especially in serum, bone, kidney and intestine. Large amounts of alkaline phosphatase are excreted daily by the liver in the bile, but the mechanism underlying changes occurring in the serum alkaline phosphatase in hepatic and biliary tract disease is not completely understood.

The serum alkaline phosphatase was estimated in all but one case of virus hepatitis and two of posthepatic jaundice. In the case of hæmolytic icterus the serum alkaline phosphatase was normal. Except in the patient with primary carcinoma of the liver, values below 35 K.U. were found in all of the cases of hepatic jaundice. On the other hand, in all of the patients with extrahepatic obstructive jaundice the serum alkaline phosphatase was found to be above 40 K.U. The average value for hepatic jaundice was 22.6 K.U., as compared to 69.5 K.U. in posthepatic jaundice.

Since first proposed by Roberts,[27] this test as a differential diagnostic aid in jaundice has had its protagonists[28] and detractors.[12] Gutman and Hanger[29] found this determination of definite value in the differential diagnosis but emphasized that the test failed to indicate common duct obstruction in almost ¼ of their proved cases of choledocholithiasis and that there was about 15% overlapping of values in the hepatic and posthepatic groups of jaundice. It is well known that the determination is not applicable in the presence of certain bone diseases and that careful and consistent laboratory technique is essential.

Cephalin cholesterol flocculation tests.—This test consists of adding a colloidal suspension of cephalin and cholesterol to the patient's serum diluted 1:21 with normal saline and then after twenty-four hours noting the degree of flocculation and precipitation of liquids in the test tube.[21] The sera of normal individuals, or of patients with diseases not accompanied by active liver disturbances, cause no or slight (1+) flocculation. Significantly positive reactions (2 to 4+) are apparently due to changes in the globulins, particularly the euglobulin fraction of the serum,[23] occurring with certain types of inflammatory and degenerative liver derangements.

In the one case of hæmolytic jaundice, the C.C.F.T. was negative. In 15 of 17 cases of hepatic jaundice, the C.C.F.T. was 2 to 4+. In the two remaining cases of virus hepatitis, the C.C.F.T. was negative throughout the entire illness in one, and became 2+ when jaundice had almost subsided in the other. On the other hand, in 11 of 12 cases of extrahepatic obstruc-

tive jaundice, the C.C.F.T. was negative throughout the entire illness. A 3+ flocculation was observed in the case due to lymphosarcoma but the clinical impression and the other laboratory tests were indicative of an extrahepatic obstructive jaundice.

Gutman and Hanger found this test very valuable in distinguishing hepatic from posthepatic jaundice, but emphasized that a negative C.C.F.T. occurred in some cases of rapidly subsiding infectious hepatitis; while cholangitis, accompanying extrahepatic obstructive jaundice might cause sufficient disturbance of the liver parenchyma to produce a weakly positive test.

DISCUSSION

As we have emphasized, an early and accurate diagnosis can be made on the clinical manifestations in the majority of cases. In doubtful cases, certain liver function tests are very helpful. In our experience the most reliable of these are the cephalin cholesterol flocculation tests and the serum alkaline phosphatase. As noted above, in all of the patients with extrahepatic obstructive jaundice, the serum alkaline phosphatase was above 40 K.U., while the cephalin cholesterol flocculation test was negative in all but one. In all but one of the cases of hepatic jaundice, the serum alkaline phosphatase was below 35 K.U. and the cephalin cholesterol flocculation test was 2 to 4+ in all but two. As has also been noted by Gutman and Hanger,[30] these tests are of great diagnostic value when they afford complementary evidence of the same type of jaundice.

There will be some cases in which a diagnosis cannot be made after the clinical picture and extensive laboratory investigation has been carefully considered for a period of three weeks. We do not agree with Giansiracusa and Althausen[12] that management of these cases should consist of supportive and symptomatic treatment for a period of two months to be followed by exploratory laparotomy if jaundice does not subside. We have found, as have others[22, 30] that by needle biopsy a careful histopathological study of liver disease can be made, and not only is one able to determine whether the jaundice is "medical" or "surgical" but frequently the type and the stage of the disease present may be ascertained as well. It is a procedure not to be taken too lightly, but in experienced hands and performed on hospitalized patients with typed blood available in case of hæmorrhage, we feel it is an easy procedure of the utmost value for early and accurate diagnosis in jaundice.

SUMMARY

1. A study of 30 cases of jaundice has been presented.

2. The importance of the history, physical examination and clinical manifestations in determining the cause of jaundice has been stressed.

3. We have found the serum alkaline phosphatase and cephalin cholesterol flocculation tests of great value in distinguishing hepatic from extrahepatic obstructive jaundice.

4. The use of liver biopsy in difficult diagnostic problems is recommended.

We would like to thank Dr. P. Rutherford, Miss Rachel Paul, Miss Grace Thompson, and other members of the Laboratory Staff for their technical assistance.

REFERENCES

1. WINTROBE, M. M.: Clinical Hæmatology, Lea and Febiger, Philadelphia, 2nd ed., p. 208, 1946.
2. DUCCI, H.: *J. Am. M. Ass.*, **135**: 694, 1947.
3. HANGER, F. W.: In Textbook of Medicine, Cecil, Saunders, Philadelphia and London, 7th ed., p. 855, 1947.
4. FLOOD, C. A., SEEGAL, D., SPOCK, B. AND LOBB, R. F.: *Am. J. M. Sc.*, **185**: 358, 1933.
5. NEEFE, J. R.: *Med. Clin. North Am.*, **30**: 1407, 1946.
6. BERK, E. J.: *Arch. Int. Med.*, **68**: 525, 1941.
7. SINCLAIR, J. C. AND FARQUHARSON, R. F.: *Med. Clin. North Am.*, **32**: 443, 1948.
8. GAMBILL, E. E.: *Proc. Staff Meet. Mayo Clin.*, **22**: 537, 1947.
9. FRENCH, H.: Index of Differential Diagnosis of Main Symptoms, 6th ed., p. 412, 1945.
10. WATSON, C. J.: In Textbook of Medicine, Cecil, Saunders, Philadelphia and London, 7th ed., p. 888, 1947.
11. MALLORY, T. B.: *J. Am. M. Ass.*, **134**: 653, 1947.
12. GIANSIRACUSA, J. E. AND ALTHAUSEN, T. L.: *J. Am. M. Ass.*, **134**: 589, 1947.
13. WHIPPLE, A. O.: In Textbook of Medicine, Cecil, Saunders, Philadelphia and London, 7th ed., p. 855, 1947.
14. MALLOY, H. J. AND EVELYN, K. A.: *J. Biol. Chem.*, **119**: 481, 1937.
15. TODD, J. C. AND SANFORD, A. H.: Clinical Diagnosis by Laboratory Methods, 10th ed., p. 111, 1944.
16. WATSON, C. J. AND HAWKINSON, V.: *Am. J. Clin. Path.*, **17**: 108, 1947.
17. KINGSLEY, G. R.: *J. Lab. Clin. Med.*, **27**: 840, 1942.
18. BLOOR, W. R.: *J. Biol. Chem.*, **24**: 227, 1916.
19. WINTROBE, M. M.: Clinical Hæmatology, Lea and Febiger, Philadelphia, 2nd ed., p. 468, 1946.
20. KING, E. J. AND ARMSTRONG, A. R.: *Canad. M. A. J.*, **31**: 376, 1934.
21. HANGER, F. M.: *J. Clin. Invest.*, **18**: 261, 1939.
22. SHERLOCK, S. P. V.: *J. Path. Bacteriol.*, **58**: 523, 1946.
23. DAUPHINEE, J. A. AND CAMPBELL, W. R.: *Med. Clin. North Am.*, **32**: 455, 1948.
24. CANTAROW, A. AND TRUMPER, M.: Clinical Biochemistry, Saunders, Philadelphia and London, 3rd ed., p. 157, 1945.
25. *Idem*: Clinical Biochemistry, Saunders, Philadelphia and London, 3rd ed., p. 428, 1945.
26. *Idem*: Clinical Biochemistry, Saunders, Philadelphia and London, 3rd ed., p. 425, 1945.
27. ROBERTS, W. M.: *Brit. M. J.*, 3773, 734, 1933.
28. MACLAGAN, N. F.: *Brit. M. J.*, 4518, 197, 1947.
29. GUTMAN, A. B. AND HANGER, F. M.: *Med. Clin. North Am.*, **25**: 837, 1941.
30. VOLWILER, W. AND JONES, C. M.: *New England J. Med.*, **18**: 651, 1947.